Third European Society of Endodontology (ESE) research meeting: ACTA, Amsterdam, The Netherlands, 26th October 2018: Deep Caries and the Exposed Pulp: Current and Emerging Therapeutic Perspectives

Duncan, H F ; Bjørndal, L ; van der Sluis, L ; Rechenberg, D K ; Simon, S ; Cooper, P R ; Ricucci, D ; Galler, K

Abstract: The overarching aim of the 3rd European Society of Endodontology (ESE) Research Meeting held in ACTA, Amsterdam on Friday the 26th October 2018 was to provide participants with an update on management of the deep carious lesion and vital pulp treatments (VPT). This theme was selected for the meeting due to significant current scientific interest in this area and because the maintenance of pulp vitality and the promotion of minimally invasive biologically based management strategies are of fundamental importance to the future of Endodontology. The principal objectives of the meeting were to understand the current evidence-base and to highlight any gaps in knowledge related to carious tissue management and handling of the exposed pulp, to determine the priorities for future research and to develop a European endodontic research group by engaging practitioners, scientists and multicentred networks. Finally, the funding of future research in the deep caries and vital pulp area was to be considered and discussed. To that end a group of European leaders, both clinical and science-based, actively working in the cariology, VPT and pulp biology fields made short presentations aimed at stimulating conversation, highlighting problems, establishing targets and developing consensus. A summary of the presentations are included below.

DOI: https://doi.org/10.1111/iej.13059

EDITORIAL

THIRD EUROPEAN SOCIETY OF ENDODONTOLOGY (ESE) RESEARCH MEETING: ACTA, AMSTERDAM, THE NETHERLANDS, 26th OCTOBER 2018

DEEP CARIES AND THE EXPOSED PULP: CURRENT AND EMERGING THERAPEUTIC PERSPECTIVES

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INTRODUCTION

The overarching aim of the 3rd European Society of Endodontology (ESE) Research Meeting held in ACTA, Amsterdam on Friday the 26th October 2018 was to provide participants with an update on management of the deep carious lesion and vital pulp therapies (VPT). This theme was selected for this meeting due to significant current scientific interest in this area and because the maintenance of pulp vitality and the promotion of minimally invasive biologically based management strategies are of fundamental importance to the future of Endodontology. The principal objectives of the meeting were to understand the current evidence-base and to highlight any gaps in knowledge related to carious tissue management and handling of the exposed pulp, to determine the priorities for future research and to develop a European endodontic research group by engaging practitioners, scientists, multi-centered networks. Finally, the funding of future research in the deep caries and vital pulp area was to be considered and discussed. To that end a group of European leaders, both clinical and science-based, actively working in the cariology, VPT and pulp biology fields made short presentations aimed at stimulating conversation, highlighting problems, establishing targets and developing consensus. A summary of the presentations are included below;

Lars Bjørndal - Management of deep caries, running multi-centred trials and unanswered questions: To improve the evidence and quality of clinical guidelines on VPT, adequately powered, well-designed, randomised clinical trials of high quality are required. At present, clinical trials regularly compare pulp-capping materials; however, the relative invasiveness of individual pulp therapies are rarely examined. As a result, patients often receive different treatments even though their dental history seems identical, ranging from selective carious tissue removal through VPT even to pulpectomy. Comparisons between different types of pulp therapy (*e.g.* stepwise excavation, pulp capping) are needed. It is imperative that such studies use the same inclusion and exclusion criteria, as well as (when possible) shared outcome measures. For example, a clear distinction of the depth of carious penetration judged radiographically, being either deep (*i.e.* pulpal quarter with a radiolucent dentine present) or extremely deep (*i.e*. passing through the entire thickness of dentine) may be an underestimated variable, that needs to be controlled in future VPT studies. In addition, the profession may benefit from a subdivision of pulp capping depending on pulpal condition with

class I pulp capping being treatment of seemingly sound pulp, while class II pulp capping is treatment of an infected pulp. Class II requires a much more complex protocol (*e.g*. magnification and disinfectant) and may in reality be best performed by an endodontist. Finally, consensus and clarity on terminology is required, as it has demonstrated that teeth exhibiting so-called irreversible pulpitis can be treated by preserving at least part of the pulp; this indicates an outdated terminology.

Luc van der Sluis: Minimally invasive endodontics - A new diagnostic system for assessing pulpitis matched to subsequent treatment needs: Managing cavitated carious lesions should use methods aimed at biofilm removal and control. Carious tissue is removed purely to establish conditions facilitating placement of a long-lasting restoration. Bacterially contaminated or demineralised tissue close to the pulp can be left *in situ*. Developments in our understanding of pulp biology and the response of the pulp to the release of dentine-bound bioactive growth factors have highlighted that the pulp in mature teeth has a greater regenerative capacity than previously thought. To ascertain the state of the pulp, the signs and symptoms observed should dictate the treatment modality based on a clinical pulpal diagnosis and not on caries progression. Often with partial removal of inflamed pulp tissue, the remainder of the pulp can heal and vitality be maintained. Preserving all or part of the pulp is beneficial as it is less invasive than conventional root canal treatment, while retaining the biological immune response and preventing apical periodontitis. Recent correlations between histological findings and corresponding clinical signs, symptoms and tests can be used to carefully differentiate between different stages of reversible and irreversible pulpitis. In addition, it has become evident that if the correct vital pulp treatment is employed, pulp tissue previously diagnosed as irreversibly inflamed can at least be partially maintained. This highlights a problem with the existing diagnostic classification system in that the use of the term “irreversible” is misleading. Therefore, future priorities should be to i) introduce a new way of diagnosing pulpitis and to ii) relate the diagnosis with minimal invasive treatment choices dictated by the degree of pulpal inflammation.

Dan Rechenberg - New age pulpal diagnostics: can we accurately determine the state of the pulp if exposed or not? As the society ages, the desire to retain teeth challenges the established doctrines, by promoting prevention and minimal invasive techniques. In this

context, and considering recent advances in biomaterials, vital pulp therapy must be re-evaluated. The success of this approach greatly depends on i) the absence of microorganisms, and ii) the pulps immuno-competence/absence of inflammation. Unfortunately, both aspects cannot be reliably determined clinically. Current pulpal tests, *e.g.* sensitivity tests towards thermal or electric stimuli, neither reliably reflect the histopathological condition of the pulp, nor enable a consistent prediction of the likelihood of pulpal survival after tooth restoration. This limitation also has an impact on the clinical terminology of pulpal inflammation, which inevitably remains imprecise. There is a pressing need to find novel ways or tools for more precise, but clinically applicable pulpal diagnosis. Potential solutions to this clinical problem may involve the application of rapid molecular tests targeting biomarkers of pulpal inflammation. Alternatively, improved imaging techniques aimed at visualizing the pulpal soft-tissue and/or blood flow as indicators for pulpal vitality. The development of these next-generation diagnostic tests in endodotnics although critical, is not without significant practical, scientific, cost and technical challenges.

Stephane Simon - Does pulp chamber pulpotomy represent the future of endodontics: The prognosis of pulp capping treatment is highly dependent of two principle factors; firstly the inflammatory status of the pulp, and secondly the quality of mineralised bridge at the interface between the pulp surface and the biomaterial. Pulpitis is a progressive disease and it is challenging clinically to establish the border between healthy and inflamed tissue. Full pulp chamber pulpotomy may be a potential solution in the treatment of pulpitis as all the pulp is removed from the pulp chamber, leaving only the pulp tissue in the root canal system, in which the tissue is generally free of inflammation. Currently, several case reports and case series have highlighted the considerable potential of this technique as an alternative to pulp capping or pulpectomy; however, the absence of a pulp response to conventional sensibility testing and the lack of comparative clinical trials suggest the need for further research to validate the treatment.

Paul Cooper - A basic-scientist's view of research in dentine-pulp complex biology: In endodontics, translational research is increasingly becoming more important and it is essential that high-quality research underpin the development of novel-therapeutic-approaches. Clinical observations have identified dentine chips arising from operative debris

are bio-stimulatory for dentine repair process. Subsequent studies have confirmed the presence of a range of potent morphogens and growth factors (GFs) as being sequestrated within the bioactive dentine and these can be released by materials routinely used in endodontic applications, such as EDTA, calcium hydroxide and mineral trioxide aggregate (MTA). Basic science studies have demonstrated that the release of these GFs locally within the tooth by these materials likely stimulate reparative events including stem cell homing, proliferation, odontogenic differentiation and increase mineral deposition. Notably the activity of these morphogens could be enhanced by degradative enzyme activity, *e.g.* matrix metalloproteinases, present in the diseased environment. Basic science studies aimed at drug repurposing have also shown that pharmaceuticals *in vitro* can also modulate odontogenic events including differentiation of stem cells and rates of dentinogenesis. Indeed, pharmacological modulators of the p38 MAP kinase pathway as well as Histone deacetylase inhibitors (HDACis) have the potential to be applied in the future in endodontics for patient benefit. Sustained basic science research is required to fuel the pipeline to provide both the experimental tools, including identifying markers for odontogenic differentiation processes, and enabling the development of novel approaches for endodontic diagnostics and treatment. Genuine clinician-scientist research partnerships are therefore required which enable bi-directional exchange of ideas and techniques. Layered on top of this is the requirement for inter-disciplinary research, which utilises methodologies in both the physical and biological sciences, as well as international collaborations which further enhance the exchange of ideas and technologies.

Domenico Ricucci - Are we really regenerating the dentine-pulp complex with preventive endodontics measures? In the presence of deep caries close to the pulp chamber, the clinician is often uncertain whether the bacteria have penetrated into the pulp tissue and establishment of a minor area of necrosis. Although signs and symptoms may help in the majority of cases to establish the pulp as ‘reversibly’ or ‘irreversibly’ inflamed, bacterial penetration may occur in the absence of symptoms. When a carious pulp exposure occurs, as long as the diagnosis is of reversible inflammation, an attempt can be made to maintain pulp vitality through a direct pulp-capping procedure. If diagnosis is irreversible pulpitis diverging treatment plans, mostly based on the severity of symptoms, have been suggested as an alternative to pulpectomy. It is recommended that the deepest part of the cavity and the

exposed pulp be clinically observed under magnification (*e.g.* operating microscope), as this can inform the successive treatment decision. Histological analysis performed in sound and carious teeth and in teeth subjected to pulp capping and pulpotomy using a range of pulp capping materials, has not equivocally demonstrated the superiority of MTA and other calcium-silicate materials over calcium hydroxide. There is a need for further research on the pulpal response to various material sin sound and carious teeth.

Henry Duncan - VPT materials - development of the next generation of biomaterials aimed at biological processes: Concerns over the cost and destructive nature of dental treatment have led the profession to examine novel methodologies that develop regenerative treatments and promote minimally invasive, biologically based dental restorative solutions. Although an exciting opportunity, vital pulp treatment has traditionally been damned by unpredictable results. Recent dental biomaterial advances, as well as an evolving understanding of molecular biology and regenerative medicine have led to the development of new treatment strategies for the exposed pulp. Calcium-silicate cements now represent the gold standard capping material, but stimulate repair non-specifically and have practical limitations including setting time and discolouration. An improved understanding of the cellular regulators of pulpal inflammation/repair is critical in order to predict pulpal response and devise a new generation of targeted dental restorative materials aimed at biological processes. However, what is possible and what is unrealistic? A wealth of *in vitro* and biological research investing the use of a range of anti-oxidants, anti-hypertensive as well as pharmacological inhibitors (*e.g*. GSK3) and epigenetic modifiers (*e.g.* HDACis) have highlighted the potential for a targeted approach to promote pulpal repair processes. Although considerable opportunity exists for development of next-generation focused biomaterials, containing these additives, several obstacles also exist in the form of designing an efficient delivery model, controlling potential off-target influences, minimising side effects and, perhaps the most significant barrier, regulatory approval. In the future close relationship between sciences, clinical dentistry and industry need to be forged in order to secure the funding necessary to develop these novel materials.

Kerstin Galler - Disinfection, irrigation and maximising the influence of dentine in vital pulp treatments - Dentine matrix proteins: Although dentine has been identified as a bioactive

matrix, which harbours a plethora of signalling molecules accessible during excavation or cavity preparation, this knowledge has not been clinically integrated into VPT procedures. Several hundreds of matrix-bound proteins are present in dentine, among them cytokines, neurotrophic and angiogenic factors, as well as other GFs. They can be released by demineralisation (*e.g.* by endodontic irrigation solutions) and subsequently modulate the immune-response as well as the migration, proliferation, differentiation and mineralisation capabilities of dental pulp cells. Dentine matrix proteins might thus facilitate healing and repair after vital pulp treatment. Different approaches are potentially available, including the simple use of EDTA to allow for endogenous GFs release until the point of pharmacologic interventions and the use of allogenic extracted dentine matrix proteins. Whereas these ideas seem feasible and are supported by *in vitro* and *in vivo* research data, generation of clinical evidence will be a major hurdle prior to application of such concepts into practice.

THE 'NEXT STEPS' AND CONCLUDING REMARKS

The treatment of deep caries and the exposed pulp stimulates considerably diversity of opinion, but a shared view that endodontic treatment should be less invasive and more biologically based. At present it is accepted that much of the evidence that we rely on to make fundamental decisions regarding vital pulp management strategies is weak (Swedish Council on Health Technology Assessment 2010, Ricketts *et al*. 2013) and that well-planed, high quality - clinical and scientific - research is required to bring the discipline forward (Duncan *et al*. 2016). The International Endodontic Journal has recently published a review article and an ESE position statement on the management of deep caries and the exposed pulp in order to highlight the current position and future focus in this area (Bjørndal *et al*. 2019, Duncan *et al*. 2019). There is an obvious need to carry out large, adequately powered randomised clinical trials, but this demands significant communication between several research centres, clinical trial units, statisticians and the development of practice-based networks. Additionally, the development of new diagnostic tools to assess pulpitis, understanding the nature of the cellular response in pulpitis and after pulp capping, as well as harnessing therapeutically dentine matrix proteins and pulp cell responses will require significant collaboration between clinicians, scientists and several institutions. All these will require funding, which remains a constant challenge at a national and European level. Researchers need to exploit available local and national resources initially, which will enable the early development of innovative

approaches necessary for the field to move forward before working collaboratively with professional bodies, other institutions and grant awarding agencies to secure the level of strategic funding to carry out high quality research in this field.

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